Declaration of Delgado

Exhibit D

IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF TENNESSEE

PLANNED PARENTHOOD OF TENNESSEE AND NORTH MISSISSIPPI, MEMPHIS CENTER FOR REPRODUCTIVE HEALTH, KNOXVILLE CENTER FOR REPRODUCTIVE HEALTH, FEMHEALTH USA, INC., d/b/a CARAFEM, and AUDREY LANCE,	)	
Plaintiffs,	)	
v.	)	**Case No. 3:20-cv-00740**
	)	**Judge Campbell**
HERBERT H. SLATERY III, Attorney General of Tennessee, in his official capacity; LISA PIERCEY, M.D., Commissioner of the Tennessee Department of Health, in her official capacity; RENE SAUNDERS, M.D., Chair of the Board for Licensing Health Care Facilities, in her official capacity; W. REEVES JOHNSON, JR., M.D., President of the Tennessee Board of Medical Examiners, in his official capacity; HONORABLE AMY P. WEIRICH, District Attorney General of Shelby County, Tennessee, in her official capacity; GLENN FUNK, District Attorney General of Davidson County, Tennessee, in his official capacity; CHARME P. ALLEN, District Attorney General of Knox County, Tennessee, in her official capacity; and TOM P. THOMPSON, JR., District Attorney General for Wilson County, Tennessee, in his official capacity,	)	
Defendants.	)	

DECLARATION OF DR. GEORGE DELGADO

I, George Delgado, M.D., pursuant to the provisions of 28 U.S.C. § 1746, do hereby declare as follows:

1. I am a physician, licensed by the Medical Board of the State of California since 1989. I submit this declaration in opposition to Plaintiffs' motion for preliminary injunction. I have personal knowledge of the matters set forth below, and could and would testify competently to them if called upon to do so.

Professional Background

2. I graduated from St. Mary's College of California with a Bachelor of Science degree, summa cum laude and received my Doctor of Medicine degree from the University of California, Davis. I completed my family residency at Santa Monica Hospital/UCLA and I am board certified in family medicine and hospice and palliative medicine. Since 2005, I have been the medical director of a family medical group. Additionally, I am the chief medical officer of a large hospice. (My CV is attached as an exhibit to this Declaration).

3. In the past four years, I have not testified as an expert in court cases. I have been asked by the Tennessee Attorney General to opine regarding this case, U.S. District Court Case No. 3:20-cv-00740, a legal action brought challenging a Tennessee law requiring abortion providers to inform medication abortion patients "that it may be possible to reverse [the] intended effects" of mifepristone, the first drug taken, "if the second pill or tablet [misoprostol] has not been taken or administered." I am being compensated, pursuant to an expert services contract, at four hundred dollars ($400.00) per standard hour worked, and will be compensated the same for testimony given at any deposition, hearing, or trial of the lawsuit, plus seventy-five dollars ($75.00) per hour for any required travel time on other days.

Background regarding Challenge to Tennessee's APR Law

4. My experience over the last 11 years helping women who wish to reverse their mifepristone medical abortions —a process often called "abortion pill reversal," through the Abortion Pill Reversal ("APR") or Rescue network—has been that women are not informed that reversal is an option. In fact, women often first call the abortion centers where they took the mifepristone in order to seek information about what may be done to stop a medication abortion. Unfortunately, they are often told "your baby is sure to have birth defects" or "there is no possibility of stopping the abortion." The medical literature and my experience have proven both statements to be false. The workers at the abortion centers are either ignorant of the potential of using progesterone to reverse mifepristone medical abortions or they are lying to the women who desire a second chance at choice after taking mifepristone.

5. For example, I saw a patient seeking abortion pill reversal on September 10, 2020 who told me that she had called the abortion center, where she had taken mifepristone (previously known as RU-486) when she had changed her mind about continuing the abortion. She was very worried because the worker there had told her that the baby would have a very high chance of birth defects if she continued the pregnancy. One hotline nurse with the APR network estimates that about one-third of the time, clients tell her that they have called the abortion center first and have been told things such as, "you must finish what you started" and "your baby is sure to have birth defects."

6. The Complaint, at paragraph 8, claims: "PPTNM's philosophy of care is to provide non-judgmental sexual and reproductive health care to all, ensuring patients receive unbiased, accurate, and complete information." If PPTNM really held to this philosophy, it would voluntarily

disclose information regarding the possibility of reversal and the fact that there is no increased risk of birth defects with exposure to mifepristone or progesterone.

7. In paragraph 9, referring to Choices Memphis, the Complaint claims: "This includes respecting patient autonomy, ensuring patients receive accurate, relevant, and unbiased information when making healthcare decisions, and providing care in a non-judgmental, supportive way." It is not respectful of patients 'autonomy if the abortion provider seeks to not disclose information based on published research and several years of experience indicating that mifepristone reversal is safe and effective.

8. In the Complaint, the plaintiffs make patently false or obsolete claims, such as in paragraph 56: "Upon information and belief, the Act's concept of ceasing, avoiding, or reversing a medication abortion is based on an experimental practice proposed by Drs. George Delgado and Mary Davenport . . . " The use of progesterone to reverse the effects of mifepristone and thus halt medical abortion is based on basic science, animal studies and studies of humans, as is explained below.

9. In the Complaint, at paragraph 58, Plaintiffs attempt to question the safety of progesterone, used for over 50 years in pregnancy: " . . . other studies have raised concerns about possible associations with second-trimester miscarriage, stillbirth, and certain birth defects . . ." This claim undermines the plaintiffs 'credibility as their two citations supporting their statements are old studies one from 2003[1] and one from 2005.[2] The 2003 study was early research on the use of 17-hydroxyprogesterone (brand name Makena) which is now approved by Food and Drug Administration (FDA) as being safe and effective for use in pregnancy to prevent preterm birth.

[1] Meiss, P. et al. Prevention of Recurrent Preterm Delivery by 17-Alpha- Hydroxyprogesterone Caproate, 348 N. Eng. J. Med. 2379, 2382 (2003).
[2] Carmichael, S. et al. Maternal Progestin Intake and Risk of Hypospadias, 159(10) Archives of Pediatric & Adolescent Med. 957 (2005)

The second study is a review of progestins and their connection to a birth defect of the penis called hypospadias. It is known that artificial progestins and not biogenetical progesterone can cause hypospadias. A 1999 FDA review concluded that there is no risk of birth defects, including hypospadias, in pregnant women taking progesterone or hyroxyprogesterone.[3] The natural progesterone administered through APR has not been demonstrated to have safety concerns for the mother or child.

Actions of Mifepristone and Progesterone

10. Mifepristone (the first of the medication abortion pills) is a progesterone receptor blocker. This action is precisely why, after it was initially synthesized, it was studied as an abortifacient. To understand why it is an abortifacient, it is important to understand the actions of progesterone. Progesterone is the hormone that is essential for the health of a pregnancy. The name was created by a German scientist, who discovered it, to convey its effect: pro-gestation.

11. Specifically, progesterone promotes the development of the maternal component the placenta (decidua basalis) and its adherence to the embryonic part of the placenta (chorion). It leads to relaxation of the uterine muscle and it prevents the formation of prostaglandins by the uterus. Prostaglandins cause the uterus to contract. Progesterone also keeps the cervix tightly closed, like a biologic valve to keep the intrauterine world safely separated from the extra-uterine world. Progesterone also stimulates milk-producing cells in the breast, leading to a sequential maturation of breast lobules. Although it prepares the breast for milk production, it actually inhibits the production of milk since milk is not needed until after the delivery of the baby, when progesterone levels naturally fall.

[3] Federal Register Volume 64, Number 70 (Tuesday, April 13, 1999) https://www.govinfo.gov/content/pkg/FR-1999-04-13/html/99-9146.htm. Accessed 13 September 2020.

12. Mifepristone is a progesterone receptor antagonist or blocker. In the same manner that a false key does not allow a door to open, when mifepristone sits on a progesterone receptor, it does not active or "open" the receptor and it does not allow the "true key," the progesterone, to latch onto the receptor.

13. By blocking the progesterone receptors, mifepristone leads to separation of the placenta from the uterus. This separation leads to a cessation of transfer of nutrients and water to the embryo or fetus from the mother, which leads to death of the embryo or fetus.

14. Additional results of progesterone blockage by mifepristone include stimulation of uterine muscular contractions. Prostaglandin synthesis, no longer inhibited by progesterone, increases and contributes to uterine contractions. With less progesterone effect, the cervix begins to soften, shorten and dilate.

15. Also mifepristone has an effect on the ovaries, which are the main sources of progesterone in the first eight to ten weeks of pregnancy. After ingestion of mifepristone, ovarian production of progesterone falls.[4] Thus there is a dual effect of mifepristone: progesterone receptors are blocked and progesterone levels decrease. These dual effects impair the action of the hormone necessary for pregnancy.

16. Three pillars of evidence support the use of progesterone to reverse the effects of mifepristone in women who choose to attempt reversal of their mifepristone abortions. Again, mifepristone was studied and approved as an abortifacient precisely because it blocks the actions of progesterone.

[4] Baulieu, E. Contragestion with RU-486: A new approach to postovulatory fertility control. Acta Obstet Gynecol Scand Suppl. 149: 5-8, 1989.

Biologic Logic

17. It is known that progesterone and mifepristone are in direct competition at the receptor level. Neither binds permanently; they each move on and off the receptor. In all biologic systems where you have molecules competing for receptors, if you increase the concentration of one, it will win the race to the receptor. The same will occur with progesterone and mifepristone. If we increase progesterone levels through supplementation, it will out-compete the mifepristone and land on and activate the receptor, leading to all of the good progesterone effects such as maintaining the adherence of the placenta.

Animal Studies

18. Early in the research on mifepristone, Yamabe and colleagues conducted experiments on pregnant rats. One group was given mifepristone only and the other group was given mifepristone and progesterone. In the group that only received mifepristone, only 33% of the pups survived. In the group that received mifepristone and progesterone, 100% of the pups survived. Furthermore, the first group had characteristic changes in the myometrium and ovaries; the group that received the combination had no such changes.[5]

Research in Humans

19. The most important medication abortion reversal study in humans was the one published by our professional group in the peer-reviewed journal Issues in Law and Medicine.[6]

20. In that study we evaluated 261 successful mifepristone reversals that resulted in live births. We found that those women who took progesterone orally using what is now called the high dose protocol had a 68% rate of reversal of the mifepristone—that is, continued the pregnancy

[5] Yamabe, S; Katayana, K; Mochuzuki, M Folio endocrine. 65, 497-511, 1989. The Effects of RU486 and Progesterone on Luteal Function During Pregnancy.
[6] Delgado, G. et al. A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone. Issues in Law & Medicine, Volume 33, Number 1, 2018.

resulting in live birth. This is compared to a historical estimated 25% embryo survival rate in the early mifepristone-only studies. The difference between the two groups was statistically significant, which means that difference in survival rates was not due to chance. In practice these days, the high-dose natural progesterone protocol is by far the predominant one being used by medical practitioners.

21. Our study also looked at safety. There was no increased risk of defects or preterm delivery in the babies born after reversal using progesterone treatment. In our study, the preterm birth rate was only 2.5%. This compares quite favorably with the 10% preterm rate in the general population.

22. Our finding of no increase of birth defects was consistent with previous research on mifepristone. In fact, the American College of Obstetricians and Gynecologists (ACOG) issued a practice bulletin in March 2014 stating that mifepristone does not cause birth defects.[7]

23. Progesterone has been used safely in pregnancy for more than 50 years. In fact, reproductive endocrinologists—the in vitro doctors—routinely give progesterone to all of their patients that achieve pregnancy.[8]

The Control Group

24. A review by Dr. Mary Davenport, et al., found that 18 of the 30 articles investigating mifepristone monotherapy (without misoprostol) had adequate criteria to determine embryo survival.[9] After eliminating duplicate publications, 12 studies were identified which utilized follow-up ultrasound to distinguish between incomplete or missed abortion and embryo

[7] Medical Management of First Trimester Abortion. ACOG Practice Bulletin 143 March 2014, reaf- firmed 2016.
[8] ASRM Practice Committee Document. PROGESTERONE SUPPLEMENTATION DURING THE LUTEAL PHASE AND IN EARLY PREGNANCY IN THE TREATMENT OF INFERTILITY: AN EDUCATIONAL BULLETIN. https://store.asrm.org/Store/Product-Details/productId/210977. Accessed 13 September 2020.
[9] Davenport M, Delgado G, Khauv V. Embryo survival after mifepristone: review of the literature. Issues in Law and Medicine 2017, 32 (1): 3-18.

survival at the end of the study period. The mean percentage of embryos surviving mifepristone among all studies was 12.6%. A single dose of 600 mg in five studies of early gestations 42-49 days in 493 subjects showed survivals of 9.4-17.1%. Three studies of 58 women with gestations less than seven weeks, using the current predominant 200-300 mg doses, noted embryo survival rates of 10-23.3%. Four studies of 83 women included gestations up to 10 weeks, daily doses of 100-200 mg, and total doses 400-800 mg. In three of these four studies, embryo survival was less than 25%. To be conservative, in our study, we chose the figure of 25% to be our historic control for future research for embryo or fetal survival after exposure to mifepristone if neither misoprostol is given, as the second part of the medical abortion process, or progesterone is given.

Criticism of Abortion Pill Reversal

25. Mitchell Creinin, MD, and colleagues unsuccessfully undertook the first randomized control trial of abortion pill reversal.[10] Dr. Creinin seemed intent on disproving abortion pill reversal from the start; so he was not unbiased. An NPR article quoted him, “It's time for a formal study that can be definitive. I want to own that," he said.[11]

26. To his credit, Dr. Creinin designed the study based on our findings in two of our previous publications.[12] To calculate the number of women needed for the study, he performed a pretrial statistical power analysis utilizing our estimated embryo survival of 25%, if no treatment is offered as well as our demonstrated 68% birth rate with the high-dose oral progesterone protocol:

[10] Creinin, M, et al. Mifepristone Antagonization With Progesterone to Prevent Medical Abortion. Obstetric and Gynecology. VOL. 00, NO. 00, DECEMBER 2019

[11] Gordon, M. Controversial 'Abortion Reversal' Regimen Is Put To The Test. NPR. 22 March 2019.https://www.npr.org/sections/health-shots/2019/03/22/688783130/controversial-abortion-reversal-regimen-is-put-to-the-test. Accessed 13 September 2020.

[12] Delgado, G. et al. A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone. Issues in Law & Medicine, Volume 33, Number 1, 2018; Davenport M, Delgado G, Khauv V. Embryo survival after mifepristone: review of the literature. Issues in Law and Medicine 2017, 32 (1): 3-18.

"We estimated a 68% continuing pregnancy rate with oral progesterone treatment based on a report using the same dosing after mifepristone administration . . . "

27. Dr. Creinin calculated that 40 patients would be needed in order to generate statistically relevant results. Interestingly, however, he did not plan to recruit extra patients, as most studies do, to account for subjects who left the study or could not be located for follow-up. This omission creates doubt about the seriousness about completing a sound, statistically meaningful study.

28. The study supported using APR's high-dose protocol: "We chose this dosing regimen because it was the most effective option previously described in a case series of mifepristone antagonization."

29. The Creinin study was designed to have 20 patients in a treatment group and 20 in a placebo group. All of the pregnant women were to receive mifepristone in a clinic in the usual manner. Twenty-four hours later, those in treatment group would start progesterone and those in the placebo group would take a placebo pill. Neither subjects nor treating clinicians were supposed to know which subjects received the progesterone and which received placebo.

30. The study was ended early for safety reasons after 12 subjects were enrolled. Two subjects exited early. One in the placebo group, due to anxiety after she started bleeding. The other, in the progesterone group, exited due to an increase in her pre-existing nausea and vomiting.

31. According to Creinin's paper, "Three others had severe bleeding requiring ambulance transport to an emergency department." Two of them were in the placebo group. One required a suction abortion. The other in the placebo group required a suction abortion and transfusion of one unit of blood for symptomatic anemia. The study enrollment was stopped after this subject." The one in the progesterone group called the ambulance and was taken to the

emergency department. However, she "required no intervention," according to Dr. Creinin." In other words, she did not need any emergency department care for her bleeding after the failed medical abortion reversal and successful medical abortion. We note that bleeding is an expected consequence of medical abortion.

32. In summary, the Creinin study safety results were:

*Two patients required suction aspiration. Both were in the placebo group.

*The single patient in the progesterone group that went to the emergency department simply represented a reversal failure and did not need to be in the emergency department, since she "required no intervention."

*The patient requiring transfusion was in the placebo group.

*Therefore, it was the placebo, not the progesterone therapy that was unsafe.

*Mifepristone alone for abortion was unsafe, in this study.

*Attempting reversal was not proven to be unsafe.

33. Although the Creinin study did not have enough subjects to reach statistical significance, the effectiveness results are strikingly consistent with the results of our large abortion pill reversal study. If we look at the outcomes of all 12 of the women who enrolled —what is termed an "intention-to-treat analysis" — we see that 67% (four out six) that had progesterone treatment had continued pregnancies at the two week mark; i.e., they were successful mifepristone abortion reversals. In the placebo group, only 33% (two out of six) had continued pregnancies at two weeks.

34. If we only look at the ten who continued the study (not counting the two that exited early), the numbers also favor the progesterone treatment group. In the progesterone group, 80% (four out of five) had continued pregnancies at two weeks; i.e., they were successful mifepristone

abortion reversals. In the placebo group, 40% (two out of five) had continued pregnancies at two weeks.

35. In 2015, Dr. Daniel Grossman et al. published a review of our first case series of progesterone reversal of mifepristone, as well as 13 studies from the 1980s, addressing continuing pregnancies after mifepristone. The authors concluded that there was insufficient evidence to show that progesterone therapy improved survival over expectant management (doing nothing), based on the reported high ongoing pregnancy rates in some of these older studies.[13] However, closer scrutiny of the studies cited for high ongoing pregnancy rates reveals inadequate criteria for the diagnosis of continuing pregnancies, i.e., continued survival of the embryo or fetus. Many early researchers focused on an efficacy end point of complete uterine evacuation and did not distinguish missed or incomplete abortions from continuing pregnancies.[14] Furthermore, the 2015 Grossman article did not include five critical studies that documented embryo survival and erroneously included four studies that did not assess abortion failure using ultrasound. One cannot make valid conclusions regarding embryo survival after mifepristone exposure when he does include studies that document embryo survival.

36. An incomplete abortion is when the embryo or fetus has died but tissue remains in the uterus. A missed abortion is when the embryo or fetus has died but no tissue has been expelled from the uterus. What matters to women who desire a second chance at choice is whether the embryo or fetus has survived mifepristone exposure. To conflate embryo or fetus survival with

[13] Grossman D et al. Continuing pregnancy after mifepristone and "reversal" of first-trimester medical abortion: A systematic review, Contraception (2015) September 2015 Volume 92, Issue 3, pp. 206–211, DOI: 10.1016/j.contraception.2015.06.001).
[14] Davenport M, Delgado G, Khauv V. Embryo survival after mifepristone: review of the literature. Issues in Law and Medicine 2017, 32 (1): 3-18.

incomplete or missed abortion is misleading because the survival rate, if nothing is done, will be elevated.

37. Most of the criticism of mifepristone abortion reversal has been biased and or ideologically based. In fact there has never been a study that has disproven the safety or effectiveness of medical abortion reversal.

38. Not all pro-abortion physicians are against abortion pill reversal. ‘‘It makes biological sense, ’’said Harvey Kliman, MD, PhD, the director of the Reproductive and Placental Research Unit at the Yale School of Medicine who was quoted in The New York Times Magazine. ‘‘I think this is actually totally feasible.” Kliman, according to the article, “is in favor of abortion rights, and made clear he wasn’t advocating widespread use of the treatment. But if one of his daughters came to him and said she had somehow accidentally taken mifepristone during pregnancy, he said, he would tell her to take 200 milligrams of progesterone three times a day for several days, just long enough for the mifepristone to leave her system: ‘I bet you it would work.’ ’’[15]

The Abortion Pill Rescue Network

39. In 2012, because of the increasing number of requests for mifepristone reversal, with some colleagues I started Abortion Pill Reversal (APR), which consisted of a network of doctors, a telephone hotline and a comprehensive web site with information on mifepristone and medical abortion reversal. In April of 2018, Heartbeat International, a not-for-profit public service organization assumed control and renamed the project Abortion Pill Rescue. The network now

[15] Graham, R. A New Front in the War Over Reproductive Rights: ‘Abortion-Pill Reversal’. The New York Times Magazine. July 18, 2017. https://www.nytimes.com/2017/07/18/magazine/a-new-front-in-the-war-over-reproductive-rights-abortion-pill-reversal.html. Accessed 13 September 2020.

includes more than 600 doctors and other medical practitioners. Abortion Pill Rescue has documented more than 1000 successful medical abortion reversals.

40. The vast majority of women seeking a second chance at choice find Abortion Pill Rescue via an Internet search. After reading the information on the web site, those who are still interested call a 24-hour hotline. After gathering basic information and determining that the women has ingested mifepristone and does seek to reverse it, the hotline staff member connects the women to a specially trained nurse. The nurse takes a basic medical and obstetric history and confirms that the woman wants to reverse. The nurse then connects the woman to a doctor in her area in order to arrange treatment, including an ultrasound and progesterone therapy.

41. In addition to the Abortion Pill Rescue web site, there is a Facebook page for women who have previously attempted reversal and for women contemplating reversal. The comments posted on this platform have been overwhelmingly positive.

Ethics of Future Research

42. Placebo groups in studies are important when you have no idea if a treatment will be beneficial. However in the case of the reversal of mifepristone medical abortions, placebo groups would be unethical since there is very good, statistically significant evidence in animals and humans that using progesterone to reverse the effects of mifepristone is effective (see the three pillars, above). It would be unethical to randomize a woman seeking a second chance at choice to a placebo group where the best chance of embryo survival would be 25%. Furthermore, it is unethical to subject an embryo or fetus to the double jeopardy of mifepristone abortion, followed by a surgical abortion, if the mifepristone abortion is reversed.

Ethics in Practice

43. It is the ethical responsibility of a physician or other medical practitioner to provide important information to a woman seeking medical abortion, even if the practitioner is an abortion advocate. The ethical responsibility is still there, even if a woman's choice to reverse her abortion is contrary to the abortion center's business model that assumes that abortion is a great good and that no one would ever choose reversal. Currently, it appears that abortion centers and abortionists, such as the complainants, are not offering information on the safety and effectiveness of mifepristone abortion reversal, and that they are not providing the information when patients ask about reversal.

44. The Tennessee law will ensure that women who change their minds after starting mifepristone abortions will be empowered with the knowledge that they 'may" be able to reverse their abortions and that reversal attempts are safe. This important protection simply ensures that women know about the possible second chance at choice.

45. A former worker at an ambition center, named Jewels Green, has called Planned Parenthood's stance against mifepristone abortion reversal "anti-science." "If they're in the business of providing comprehensive women's health care as they claim, I don't know why Planned Parenthood would take such an anti-science stance."[16]

[16] Baklinski, P., New method to 'reverse' abortions causes outrage at Planned Parenthood. Life Site News. August 16, 2017. https://www.lifesitenews.com/news/planned-parenthood-hates-the-new-abortion-reversal-method.-its-inventors-kn. Accessed 13 September 2020.

I declare under penalty of perjury that the foregoing is true and correct. Executed by me this 13 th day of September, 2020 at Escondido, California.

GEORGE DELGADO, M.D.

Curriculum Vitae of Delgado

Attachment 1

GEORGE DELGADO, M.D., F.A.A.F.P.

November 2019

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Telephone: 760-504-2180

PROFESSIONAL GOAL:

My mission is to deliver the highest quality of individualized healthcare, develop systems that efficiently support excellence in healthcare delivery and participate in innovative clinical research, while respecting the dignity of every human person.

EDUCATION:

University of California, Davis School of Medicine, Doctor of Medicine degree 1988

Saint Mary's College of California, B.S. Biology, Summa Cum Laude 1984

RESIDENCY TRAINING:

Santa Monica/UCLA Medical Center, Family Practice July 1988 to June 1991

Certifications:

American Board of Family Medicine, recertified 2015

Hospice and Palliative Medicine, American Board of Family Medicine, certified 2010

Hospice Medical Director Certification Board, certified 2016

Health Care Ethics one-year certification program, National Catholic Bioethics Center, Philadelphia, PA 2012

NaProTECHNOLOGY one-year training program, Pope Paul VI Institute, Creighton University, Omaha, NE 2005

Fellow, American Academy of Family Physicians

Active California physician and surgeon license

Active DEA certificate

Professional Experience:

The Elizabeth Hospice, Escondido, CA 2005 to 2006, 2007 to current

Chief Medical Officer, March 2017 to present

Associate Medical Director, 2014 to 2017

Medical Director, Pediatric Hospice and Perinatal Program 2012 to present

Regional Medical Director October 2012 to 2014

Staff Physician The Elizabeth Hospice, Escondido, California 2005 to 2006, 2007 to 2012

Scripps Memorial Hospital Encinitas, per diem palliative medicine physician 2011 to May 2014

Pomerado Hospital, per diem hospitalist 2005 to 2012

George Delgado, M.D., Inc., San Diego and Escondido, California, family medicine August 2005 to present

Solano Family Physicians Medical Group, Benicia, California, co-founder and president November 1991 to June 2005.

Founder and President of The Steno Institute August 2018, clinical research

ACADEMIC APPOINTMENTS

Voluntary Associate Clinical Professor University of California, San Diego, School of Medicine, Department of Family & Preventive Medicine, May 2005 to 2012

Associate Clinical Professor, 1998 to 2005; Assistant Clinical Professor 1991 to 1998 University of California, Davis, School of Medicine, Department of Family & Community Medicine

HONORS

Service Management Citation, Santa Monica Hospital Medical Center, 1989

Saint Mary's College, Department of Biology, Carlos Freitas Award, 1984

American Association of University Women Academic Achievement Honor, 1984

American Heart Association Student Research Fellowship, 1983

PUBLICATIONS:

Delgado, Condly, et al, *A Case Series Detailing the Successful Reversal of Mifepristone Using Progesterone,* Issues in Law &Medicine, volume 33, number 1 2018

Davenport, Delgado, Harrison and Kauv, Embryo Survival After Mifepristone: A Systematic Review of the Literature, Issues in Law & Medicine, vol 32, number 1 2017

Delgado and Davenport, *Progesterone Use to Reverse the Effects of Mifepristone,* Annals of Pharmacotherapy 2012; 46

Benicia Herald: "Family Health Matters" weekly newspaper column, February 1992 to 2005.

The 5 Cs of Marriage article in *Be* magazine, May-June, 2001

Tsukamoto, French, Benson, Delgado, et al, Severe and Progressive Steatosis and Focal Necrosis in Rat Liver Induced by Continuous Intragastric Infusion of Ethanol and Low Fat Diet. Hepatology 1985; volume 5: 224-232

Tsukamoto, Delgado, et al, Effects of Cepha Stimuli, Food Intake, and Cholecystokinin on Plasma Levels of Amylase, Lipase, and Immunoreactive Cationic Trypsinogen in Rats Digestion 1986; Volume35:69-77

Tsukamoto, Sankaran, Delgado, et al, Increased Pancreatic Acinar Content and Secretion of CationicTrypsinogen Following 30 day Continuous Ethanol Intoxication in Rats Biochem. Pharmacol. 1986; volume 35:3623-3629

Tsukamoto, Delgado, et al, Molecular Forms of Trypsin in Ascites of Rats with Experimental Pancreatitis: Correlation With Mortality. Submitted to Gut

ABSTRACTS

Tsukamoto, Sankaran, Delgado, et al, Nonparallel Changes in Pancreatic Synthesis and Secretion of Amylase and Trypsin Following 30 day Ethanol Intoxication in Rats Gastroenterology 1984; volume 86: 1285

Tsukamoto, Delgado, et al, Molecular Forms of Trypsinin Ascites of Rats with Experimental Pancreatitis: Correlation With Mortality Gastroenterology 1986; volume 90: 1672

SECOND LANGUAGE

Fluent in Spanish

References furnished upon request

Yamabe Reversal

Attachment 2

The Effect of RU486 and Progesterone on Luteal Function during Pregnancy

Shingo YAMABE, Kazuaki KATAYAMA and Matsuto MOCHIZUKI

Department of Obstetricsand Gynecology,

Kobe University,School of Medicine,

Kobe, Japan

In order to investigate the role of progesterone in the maintenance of pregnancy, an anti-progesterone agent, RU486 (RU) was injected subcutaneously into pregnant rats on day12 (D12), and morphological changes of the uterus as well as endocrinological changes were observed.

In all rats injected with RU, abortion occurred with macroscopic and microscopic intrauterine hemorrhage and degeneration or delivery of conceptuses. Endocrinologically, the levels of progesterone decreased rapidly 48 hours after the injection, while the levels of estradiol showed a tendency to increase.

As progesterone is mainly produced by the corpus luteum but not by the placenta in rats, the decrease in progesterone is suspected to be due to luteolysis. Then in order to clarify the mechanism of luteolysis induced by RU and the effects of progesterone on this phenomenon, the dynamics of the luteotrophic factors (estradiol, LH, PRL) and specific binding capacity of the ovaries to LH/hCG were investigated in D7 pregnant rats treated with RU 1mg/kg alone (RU group) or with both RU 1mg/kg and progesterone 50mg/kg (RU+P group).

The serum levels of progesterone in the RU group decreased significantly after 72 hours of administration, while those in the RU+P group remained within the levels of the control group. However, serum levels of luteotrophic factors in the RU group did not decrease, and some of them were even higher than those in the control group. In the RU+P group, luteotrophic factors remained within control levels.

On the other hand, the specific bindings of LH/hCG to ovarian homogenates decreased significantly after 72 hours in the RU group. But in the RU+P group, the specific bindings were kept at the same levels as the controls. Scatchard analysis of these results disclosed that in the RU group, both affinity and numbers of receptors decreased compared to the controls, and that in the RU+P group only affinity decreased transiently and afterwards recovered quickly. From these results, it is concluded that deterioration of affinity and numbers of ovarian LH/hCG receptors seems to be one of the factors which induce luteolysis in pregnant rats treated with RU, and that progesterone can spare the effect of RU on the corpus luteum during pregnancy.

Introduction

Progesterone is considered to be essential to all mammals for the maintenance of pregnancy [1)]. Although there is still dispute concerning its mechanism and site of action, its most important functions are considered to be the suppression of endometrial prostaglandin production, the acceleration of metabolism, and uterine muscle tension relief [12) 18)].

In rat pregnancy, progesterone is produced by the corpus luteum throughout the entire period via secretions [1) 3)], but luteal function is maintained by the stimulus of the pituitary gland, the ovaries, or luteotrophic factor originating in the placenta.

This time, in a preliminary experiment, we administered the anti-progesterone drug RU486 (RU) to rats, and upon doing so not only did it induce abortion, but we observed that it also brought about a deterioration in luteal function.

Consequently, in searching for the role of progesterone with regard to the mechanism of maintenance for the rat's corpus luteum of pregnancy, in the 7th day of pregnancy, RU486 or a combination of RU486 and progesterone was administered to the rats, and we increased our scrutiny towards the action of luteotrophic factors (LH, PRL, estradiol) in the blood, as well as the important luteotrophic factors in this period, and changes in the ovarian receptors for LH.

Methodology

1. Materials

1) Rats

8-12 week old female Wistar rats (weighing 200-230 grams) were allowed to breed freely with male Wistar rats that they were reared with. Every morning at 9 AM, a vaginal smear was collected using a cotton swab, and the day that sperm was observed was designated "Day 0" (D0).

2) RU486: 17β -hydroxy-11β -(4-dimethyl-aminophenyl)17α(1-propyny1)estra-4, 9-dien-3-one

This anti-progesterone drug has 5 times the affinity of progesterone towards progesterone receptors [15)], and we received our supply from the Roussel-Uclaf company. The drug was dissolved in a 50% ethanol solution, prepared in 0.4 mg/ml doses, and used as an injection.

In addition, the crossover frequency of this drug with progesterone in RIA was found to be less than 0.1%.

2. Method

Experiment 1

Pregnant rats were administered 10 mg/kg of RU486 hypodermically in their backs between 9 AM and 11 AM of Day 12, and designated as the "D12-RU" group. A group identical

to the D12 group received an injection of just 50% ethanol, and was designated as the "D12-control" group.

24, 48, and 96 hours after injection, blood was collected by decapitation of the rats, a check was performed for whether or not abortion had occurred, and hysterectomies were conducted. The collected uteri were fixed with 10% formalin, applied with H-E stain, and examined with a microscope. The collected blood was immediately separated into serums and preserved cryogenically at -20° Celsius, and measurements of estradiol and progesterone were carried out as indicators of post-injection ovarian function. Furthermore, the rats were assigned groups and hours from n = 4 - 6.

Experiment 2

The experiment schedule is shown in Figure 1.

As with experiment 1, Day 7 rats were injected with 1 mg/kg of RU or 1 mg/kg of RU with 50 mg/kg of progesterone, then put into respective RU and RU+P groups, and a group given just 50% ethanol was designated the control group. Each group's rats were decapitated and dissected 24, 48, 72, and 96 hours after injection, and hysterectomies and oophorectomies were performed. The collected blood was immediately separated into serums, and preserved cryogenically at -20° Celsius. After the surgically removed uteri were weighed, they were cut open and inspected in order to confirm whether or not abortion had occurred. On this occasion, the separation of fetal sacs or placenta from the uterine wall was regarded as abortion. Because there existed fetal sacs which had already been discharged, the number of deciduomas on the uterine wall was estimated as the implantation count. After weighing the ovaries, they were immediately preserved cryogenically at -60° Celsius. The number of rats used in the experiment was assigned groups and hours from n = 4 - 6.

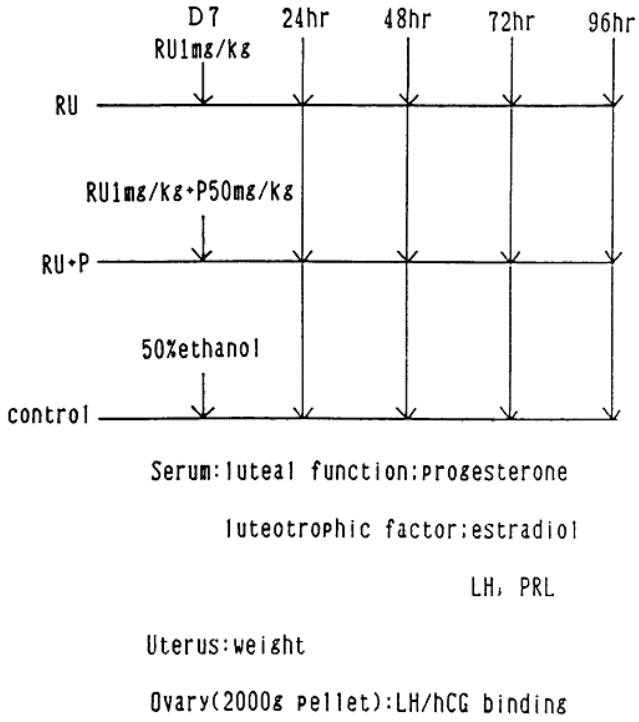

Figure 1 Experimental design. Pregnant rats were divided into three groups. Rats of each group were injected with RU 1mg/kg, both RU 1mg/kg and progesterone 50mg/kg, or ethanol only for control and were decapitated at 24, 48, 72, 96hrs. after the injection.

1) Hormone Measurement

The measurements of the serum estradiol along with progesterone were performed using the RIA measurement kit made by the Green Cross Corporation.

The measurements of LH and prolactin (PRL) were performed using RIA which used NIADDK-rLH-1-6, NIADDK-anti-rLH-S-9, NIADDK-rLH-RP-2, NIADDK-rPRL-1-5, NIADDK-rPRL-anti-S-9, and NIADDK-rPRL-RP-3 received from the provision of NIADDK.

2) Binding Experiment [14)]

After thawing the frozen ovaries, PBS was used to homogenize them; the 2000g pellets were rinsed 3 times with PBS, the receptors were demarcated, and this was supplied to the binding experiment which used hCG. This pellet was regulated in order for it to amount to 4 mg of protein per tube, and after adding ^{125}I-hCG (4000cpm) to this, the hCG was added in so as to attain concentrations of 0, 0.75, 1.5, 3.0, 6.0, 12.0, 24.0, 48.0, and 100 ng/nl, PBS was added, and the entire volume was taken as 1 ml. At room temperature, incubation was performed for 4 hours, and after centrifuging and rinsing, the radioactivity of the pellet was measured with a γ-counter. In addition, the part which had 100 ng/nl of hCG added to it was used for non-specific binding. From here, the results of this binding experiment were investigated using Scatchard analysis.

3) Examination of Statistical Significance

Statistical significance was examined by means of a Student-t test.

Results

1-1) Macroscopic and Microscopic Observations of the D12-RU Group

Figure 2 shows the findings at the time of dissection and a microscopic view of the surface of the uteri stained with H-E. "A" is 24 hours after injection, "B" is 48 hours after injection, and "C" is the findings 96 hours after injection.

Looking macroscopically, 24 hours after injection one can notice that there is only a slight degree of intrauterine punctiform bleeding, but 48 hours after injection there is a large amount of intrauterine bleeding, and 96 hours after injection, a decrease in uterine volume and an atrophy of its contents was observed. Furthermore, in the 96 hour set, it was also observed that a portion of the uterine contents had been discharged.

Looking microscopically, clear signs of abortion were not seen 24 hours after injection, but after 48 hours, retroplacental hemorrhage was observed. Furthermore, after 96 hours had passed since injection, a degeneration, withering, or discharge of conceptus were observed.

1-2) Changes in Estradiol and Progesterone in the D12-RU Group

Figure 3 shows the changes in estradiol (mean±SD). Furthermore, the check for statistical significance was performed between the RU group and the control group at each of the hours.

Estradiol was compared to the control at the 24 and 48 hour marks after RU injection, and there was a significantly high level, but at 96 hours it had returned to the levels of the control.

Figure 4 displays the changes in progesterone. Progesterone showed a declining trend from 48 hours on after injection of RU, and 96 hours after injection, it had fallen to roughly non-pregnancy levels.

2-1) The RU Group on D7, and the Abortion Rates and Changes in Uterine Weights in the RU+P Group

Figure 5 shows the changes in uterine weights of each group (mean±SD). Comparing the uterine weights of the RU group to the control group, a decreasing trend was seen from 48 hours after injection, and the 72 and 96 hour marks showed a significant decrease. On the other hand, the RU+P group showed changes in uterine weights which were approximately the same

as in the control groups. From 48 hours on after injection, the abortion rates in the rats were 66.7% in the RU group and 0% in the RU+P group, similar to the control group.

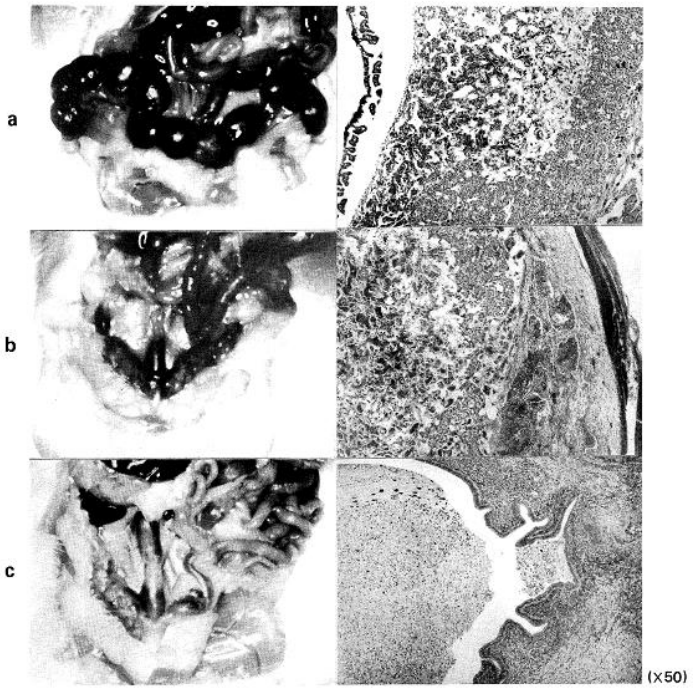

Figure 2 Morphological changes of uterus after the injection of RU on D12.
a: 24hrs. after the injection.
No evidence of abortion is found macroscopically nor microscopically.
b: 48hrs. after the injection.
Macroscopical and microscopical hemorrhage can be seen in endometrial and decidual tissues.
c: 96hrs. after the injection on D12.
Macroscopically uteri are much smaller than that at 48hrs. and some conceptuses have already been aborted. Microscopically conceptuses are degenerated and renewal of the endometrium can be seen.

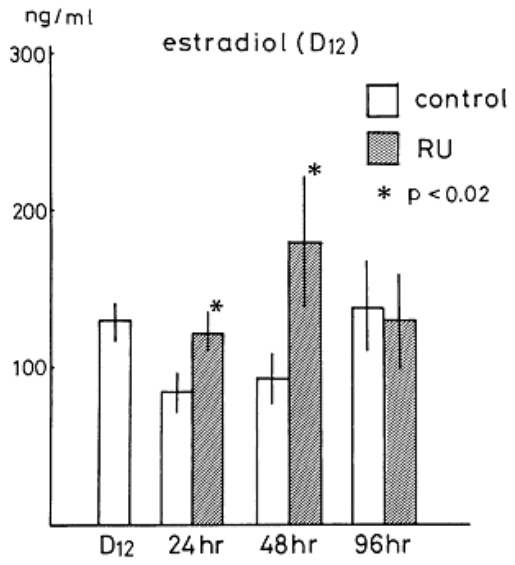

Figure 3 Levels of serum estradiol after the injection of RU486 on D12.
All results are presented as mean ± SD.
**Significant difference (p<0.01)*
Estradiol levels of D12-RU group were significantly higher than those of control at 24, 48hrs. after the injection.

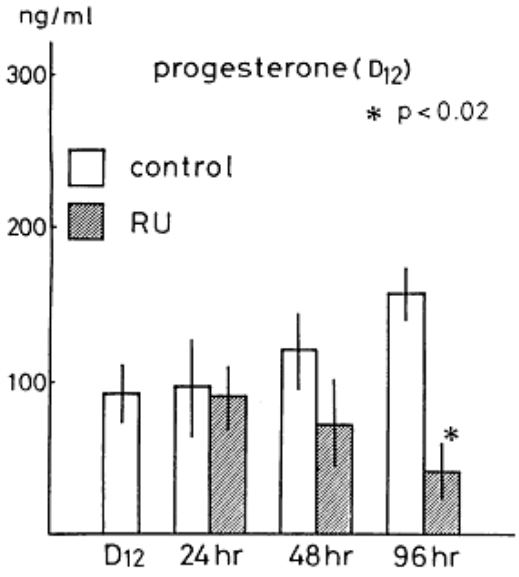

Figure 4 Levels of serum progesterone after the injection of RU486 on D12.
**Significant difference (p<0 .02)*
Progesterone levels of D12-RU group lowered significantly after 48hrs. of the injection.

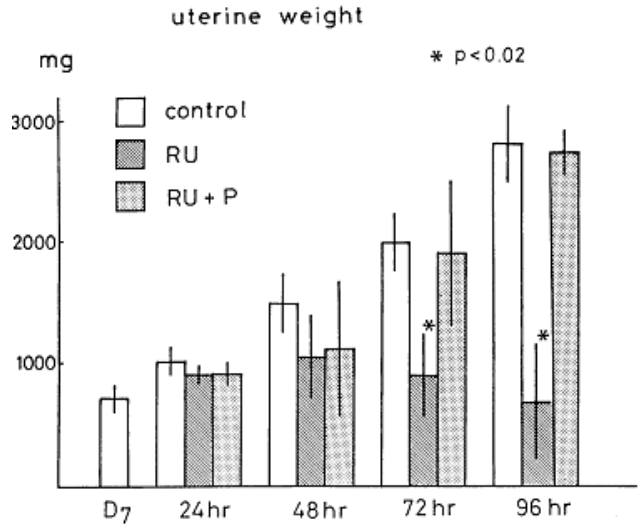

Figure 5 Uterine weights after the injection of RU486 or both RU486 and progesterone on D7.
**Significant difference (p<0.02)*
Uterine weight of RU group decreased after 48hrs. of the injection, which indicates that abortions have completed.

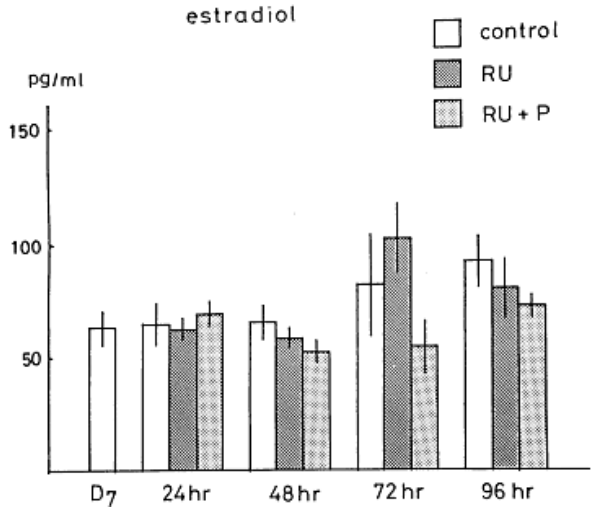

Figure 6 Levels of serum estradiol after the injection on D7.
There were no significant differences in estradiol levels between RU group or RU+P group and control.

2-2) Changes in Ovarian Function in the D7 Injection Group

Figure 6 shows the changes in estradiol after injection. In the control group, the changes in estradiol are in a roughly stabilizing state from 65.5±7.0 pg/ml before injection (D7) to 67.0±4.9 at 48 hours after injection (D9), but a rise to 82.5±22.3 was shown at 72 hours.

In the RU group, the estradiol shows changes nearly identical to those in the control group; a stabilizing state continues until 48 hours after injection, but at 72 hours the estradiol levels rose and reached a peak of 104.2±15.3 pg/ml.

In the RU+P group, the estradiol levels had decreased to 53.2±5.3 pg/ml by 48 hours after injection, and at 96 hours it returned to 74.1±3.7, roughly the same level as in the control group.

Figure 7 shows the changes in the levels of serum progesterone.

The level at D7 is before injection. The D7 progesterone level is 76.5±7.8 (mean±SD) ng/ml, and in the control group, the level is increasing to 95.3±14.7 after 96 hours (D11).

In contrast, the RU group had progesterone levels of 83.5±4.0 ng/ml at 24 hours after injecting the RU486, which indicated a trend roughly the same as the control group, but from 48 hours on it began to decrease, at 72 hours it was at 58.5±9.8, and at 96 hours it was at 57.2±15.6, which indicated a significant decrease.

In the RU+P group, the progesterone levels showed a clear increase at 24 and 48 hours after injection and gradually decreased thereafter to 93.3±13.4 ng/ml at 96 hours, which indicated levels roughly corresponding with the control.

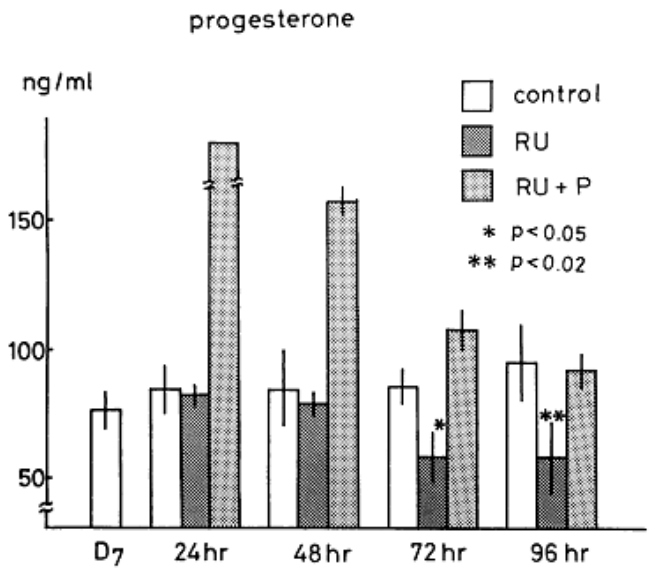

Figure 7 Levels of serum progesterone after the injection on D7 groups,
** Significant difference (p<0.05)*
*** Significant difference (p<0.02)*
Progesterone levels of RU group declined significantly after 48hrs. of the injection. But no decrease in progesterone was found even after 96hrs. of the injection in RU+P group.

2-3) Changes in PRL and LH in the D7 Injection Group

Figure 8 is the changes in pituitary LH after injection of RU. In the control, LH shows a decrease between D7 and D9 from 0.92±0.11 ng/ml to 0.45±0.07, but at D10 it increased to 0.99±0.25.

In the RU group, the LH was 1.12±0.14 ng/ml at 24 hours after injection, and 1.19±0.21 at 48 hours, which indicated an obvious increase, and it reached a peak of 1.45±0.53 ng/ml at 72 hours after injection.

In the RU+P group, the LH showed a trend practically the same as the control group up to 96 hours after injection.

Figure 9 is the movement of PRL. The control shows approximately stable levels of PRL between the 15.8±1.6 ng/ml before injection and the 19.9±4.6 at 96 hours after injection.

In the RU group, 24 hours after injection the PRL showed a level roughly the same as before injection, but from 48 hours after injection it began to increase, and it reached a peak of 23.0±5.3 ng/ml at 72 hours after injection. However, this did not show any statistical significance when compared to the control.

In the RU+P group, even though the PRL was somewhat on the low side, it showed a development that was approximately the same as the control group.

2-4) Changes in the LH/hCG Receptors of the Ovaries

Figure 10 shows the rates of change in the specific binding of ovarian homogenate towards the hCG, with the specific binding before injection being ±0%. The specific binding towards the added ^{125}I-hCG before injection (D7) was 15.4%. In the control, the specific binding gradually increased from before injection (D7) through 96 hours after injection (D11), and reached 28.4±12.1% at 96 hours after injection.

The specific binding in the RU group began to decrease from 24 hours after injection, and very clearly decreased to -29.3±13.9 at 72 hours, and -38.9±18.1 after 96 hours.

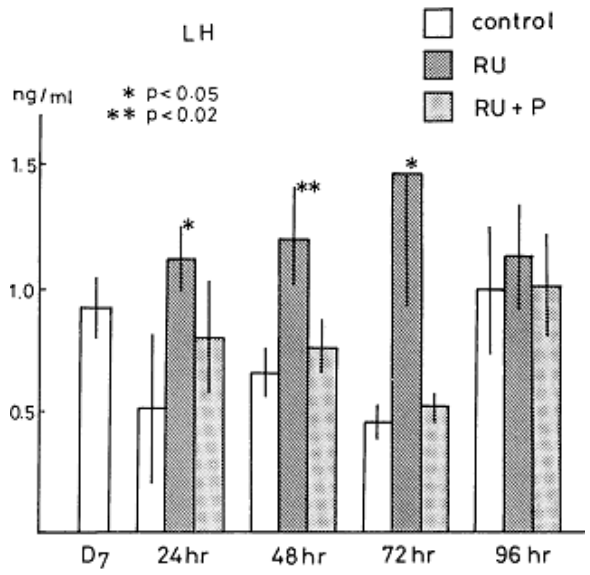

Figure 8 *Levels of serum LH after the injection on D7.*
**Significant difference (p<0 .05)*
***Significant difference (p<0 .02)*
LH levels of RU group were significantly higher than those of control at 24, 48, 72hrs. after the injection, while in the RU+P group they were almost in the same levels of control

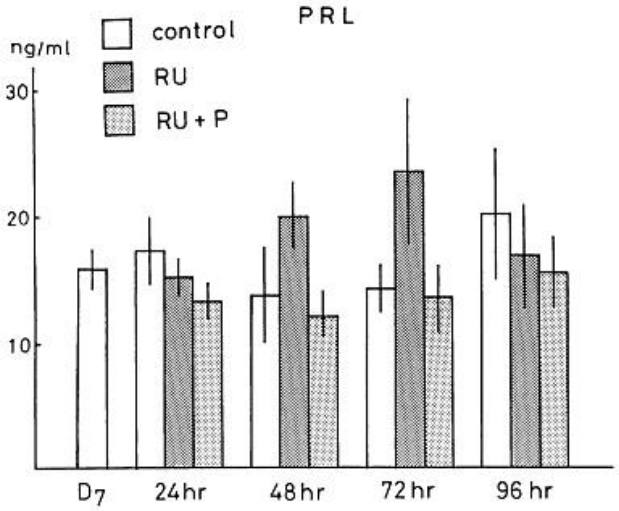

Figure 9 *Levels of serum PRL after the injection on D7.*
There were no significant differences in PRL levels between RU group or RU+P group and control.

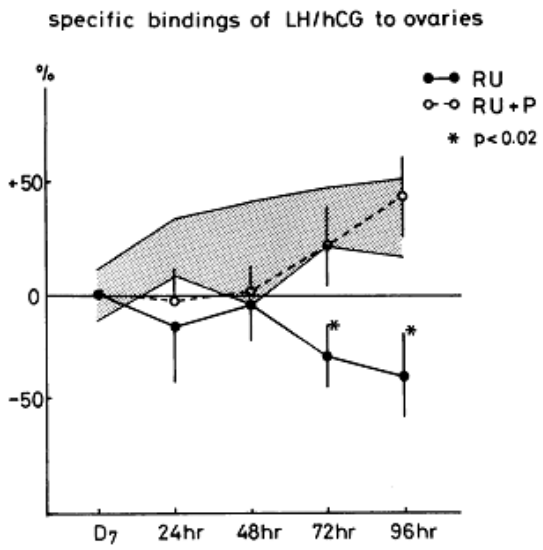

*Figure 10 Specific bindings of ovaries to LH/hCG of D7 groups. Hatched area indicates the levels of control. All data were represented by % increase and decrease. *Significant difference (p<0 .02) Specific binding of RU group decreased at 72hrs. of the injection with significant difference from those of control, while those of RU+P group were not significantly different.*

The changes in the specific binding in the RU+P group were approximately the same as the control.

Figure 11 shows the results of the Scatchard analysis on the experiment for the binding of ovarian homogenate towards hCG. The association constant in the control, shown on the top level, was $5.1x10^{9}$ before injection (D7), and $5.0x10^{9}$ at 96 hours (D11), thus not showing a large change. However, the number of receptors gradually increased from $8.5x10^{-3}$ nmol/mg prot at D7 to $18.2x10^{-3}$ at D11.

In the RU group, the association constant begins to gradually decrease from 24 hours after injection, and becomes $3.5x10^{-9}$ at 96 hours after injection. The number of receptors is $9.8x10^{-3}$ nmol/mg prot at 24 hours after injection, and shows a slight increase to $10.4x10^{-3}$ at 48 hours, but at $7.8x10^{-3}$ at 96 hours, it showed a decreasing trend when compared to before injection.

In the RU+P group, the association constant shows a clear decrease at 24 hours after injection, becoming $1.1x10^{9}$. However, the association constant gradually recovers, and becomes $5.1x10^{9}$ at 96 hours after injection, which is approximately the same level as the control. Nevertheless, this increase in receptor number did not affirm a difference 96 hours after injection between its value of $21.5x10^{-3}$ and the control (D11) level.

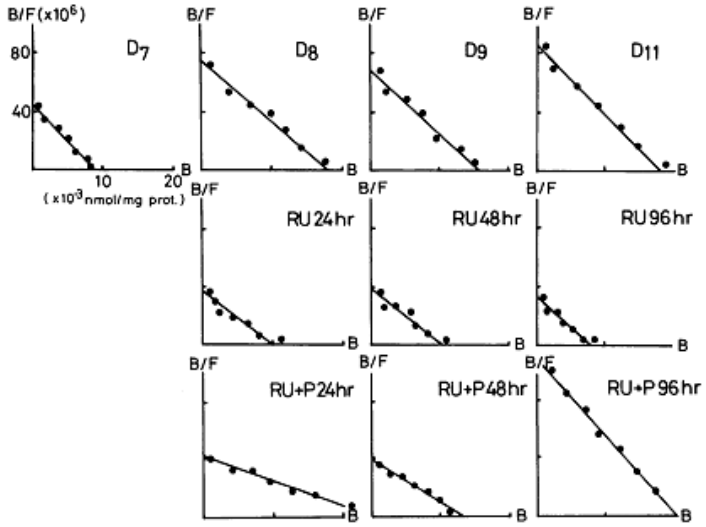

Figure 11 *Scatchard analyses of the bindings of hCG to ovaries. In control group both affinity and the number of receptors had tendency to increase along the course of pregnancy, however in RU group both of them decrease after the administration. On the other hand in RU+P group at 24hrs. the number were increased and affinity lowered but at 96hrs. both the number and affinity were at almost the same level of control.*

Design

In experiment 1, it was simple to identify conceptus for the sake of confirming the role of progesterone in the maintenance of pregnancy; rats were injected with RU in mid-term pregnancy (D12), during which the presence of the ovaries is considered to be indispensable to the maintenance of pregnancy [9) 16)], and along with investigating whether or not abortion occurred, serums of estradiol and progesterone, both indicators of ovarian function, were measured. As a result, in the rats injected with RU, endometrial hemorrhaging took place 48 hours after injection, and at 96 hours, some intrauterine content had been discharged, thus appearing that abortion had been induced.

On the other hand, looking at the steroids of the ovaries, from 24 hours after injection of RU, in spite of estradiol indicating that, if anything, it was increasing, the progesterone showed a clear decrease after injection of RU. The progesterone of the pregnant rats is for the most part produced by the corpus luteum, while the placenta at the end of term produces just a small amount [1) 3) 18)]. Considering this fact, it is thought that this reduction in progesterone is not where the discharge and degeneration of the placenta originate from, but that the corpus luteum is where this deterioration in function originates. That is, RU blocks the action of progesterone, and along with bringing about abortion, it also has an influence on luteal function, and inhibits the production of progesterone.

Accordingly, in experiment 2, to understand why the reduction in luteal function takes place with the anti-progesterone drug RU, and with the reduction in luteal function, whether or not the injection of a sufficient amount of progesterone could protect against it, we attempted to inject the RU

or the RU and progesterone on D7, when the influence of the luteotrophic factor of the placenta is largely nonexistent, and pituitary LH fulfills a much larger role as the luteotrophic factor [18) 19)].

To that end, in the group that was injected with just RU, abortion occurred in most of the rats just like in experiment 1, and a reduction in uterine weight was seen, but in the group which was injected with RU and progesterone at the same time, abortion did not occur at all, and uterine weights increased over time, the same as in the control.

Looking with regard to luteal function, in the RU group, progesterone clearly decreased after 72 hours following RU injection, the same as in experiment 1. However, in the group which was injected with RU and progesterone at the same time, even after over 72 hours had passed following injection, a decrease in progesterone was not seen. This suggests that progesterone blocks abortion caused by RU, and simultaneously operates with some sort of mechanism to also protect against the deterioration of luteal function.

From there, we attempted to investigate the movement in blood of estradiol, LH, and PRL, which are considered to show luteotrophic action [5) 18) 19)], in each of the groups of rats in this period of pregnancy.

The ovarian luteotrophic factor estradiol is, like progesterone, an indicator of luteal function. However, in the RU group, despite the decrease in progesterone, estradiol did not decrease at all; rather, it even showed an increasing trend. Furthermore, in the D12-RU group as well, a very obvious increase of estradiol was observed after injection of RU. This is thought to be the injection of RU removing the suppression of new follicles by progesterone, and the resulting start of growth, similar to the suppression of ovarian follicle growth by progesterone also found in the report of Fukuda et al [4)]. In fact, although not shown in the results, a large number of growing follicles were macroscopically seen in the ovaries of the RU group. It is also thought to be for this same reason that in the RU+P group, the estradiol takes a low level when compared to the control.

On the other hand, looking at the pituitary luteotrophic factors LH and PRL, the concentration in blood indicated a trend in the RU+P group roughly identical to the control group, but in the RU group there was absolutely no trend of decline, but it instead even showed an increasing trend. These experimental results agree with the report of Asch, Rojas [2)], and Healy [6)] et al. in which no large change was seen in the pituitary function of monkeys even after injecting them with RU during the luteal phase, and this suggests that this deterioration of luteal function in the RU group did not mediate nor cause a substantive decrease of luteotrophic factors (i.e. estradiol, LH, PRH, etc.), to say the least.

Similarly, the prevention of deterioration in luteal function with the injection of progesterone also does not seem to cause a substantive change in luteotrophic factors.

Accordingly, the binding capacity towards the most dominant luteotrophic factor of these pregnant rats in this period, LH, was examined using these rat ovaries treated with hCG. As a result, in the RU group the specific binding capacity of the ovaries to LH/hCG clearly decreased after 72 hours following RU injection, but in the RU+P group, there was an obvious increase over time, the same as in the control group.

Furthermore, when analyzing this change in binding capacity with a Scatchard analysis, in the RU group, a clear decrease in affinity and receptor number of the ovaries towards LH/hCG was indicated.

However, in the group which was injected with RU along with progesterone, at 48 hours the affinity had gradually decreased, but at 96 hours the affinity and receptor number had both returned to the same levels as the control.

This reduction of receptor number when injecting RU, similar to the findings of Hwang and Menon [7], is a phenomenon seen even in the involutional period of the corpus luteum, and so because it also disappears with the resulting deterioration of luteal function, one cannot conclude that this is the immediate cause of the deterioration of luteal function. However, even if the reduction of receptor number and the process of deterioration of luteal function were the same phenomenon, it is obvious that in this case the luteal function would further proceed to deteriorate.

At the present time, there is no definite answer as to with what kind of mechanism RU reduced receptor number, nor if it caused the deterioration of luteal function. However, judging from the fact that these functions were restored by adding progesterone, it is clear that these phenomena arose from RU obstructing the action of progesterone.

Incidentally, as for the action of progesterone toward luteal function, it is considered to act through the central endocrine system (hypothalamic-pituitary) to directly act on the peripheral endocrine system (utero-ovarian).

As for the action in the central endocrine system, it is known that the progesterone in humans and monkeys has a mechanism which exerts influence on the levels of hypothalamic-pituitary gonadotropins, especially the rhythmic secretions of LH [17) 20) 21)]. In these experiments, because we could not take frequent continuous measurements, it was not made clear, but it is thought to be possible that the aforementioned phenomena are due to RU blocking the action of progesterone in the central endocrine system and throwing the rhythmic secretions of LH into disorder.

On the other hand, progesterone is also known to have activity which inhibits [3) 8) 10)] the production of PGF2α, one of the luteolytic factors in the endometrium and myometrium [11) 13)]. No information has been found regarding the relationship between luteolysis and the PG originating in the uterus in rats, but supposing we assume that PGF2α is produced in the ovaries and that this production of PG is inhibited by progesterone, then the possibility could be not be denied that such progesterone action would be blocked by RU, the PGF2α production in the corpus lutea themselves would be accelerated, and luteolysis would be induced.

From the injection of RU, the reduction of ovarian receptor number toward LH is a direct cause of the deterioration of luteal function, the result being that this phenomenon is one that can be avoided with the injection of progesterone. From this fact, the likelihood is very high that progesterone not only prevents abortion by directly acting upon the uterus, but simultaneously contributes to the maintenance of pregnancy by protecting luteal function through some sort of mechanism.

Conclusion

From the injection of RU, it was observed that abortion was induced in D12 and D7 pregnant rats, along with a decrease in progesterone. In D7, this decrease in progesterone was not accompanied by a decrease in luteotrophic factors estradiol, LH, and PRL. However, ovarian specific binding capacity

towards LH/hCG decreased, and this indicated a possibility of being a cause of the deterioration in luteal function. Furthermore, when injecting progesterone together with RU, abortion was prevented, and the decrease in progesterone as well as the decrease of ovarian specific binding capacity towards LH/hCG was also hindered. From the above experimental results, progesterone is thought to possess some sort of protective function towards luteal function after the injection of RU during pregnancy.

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Delgado Final Case Series

Attachment 3

A Case Series Detailing the Successful Reversal of the Effects of Mifepristone Using Progesterone

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ABSTRACT:

Background: Some women who take mifepristone, a progesterone receptor antagonist, in order to terminate their pregnancies, change their minds and desire to stop the medical abortion process. There are only two articles in the medical literature documenting the reversal of the effects of mifepristone.

Objective: We present and analyze a series of women who attempted to reverse the effects of mifepristone by taking supplemental progesterone to determine if the reversal of the effects mifepristone with progesterone is possible and safe. Additionally, we compare different progesterone regimens to determine relative efficacies.

Methods: This is a retrospective analysis of clinical data of 754 patients who decided to attempt to reverse the medical abortion process after taking mifepristone but before taking the second drug in the protocol, misoprostol. We followed the patients, who were given progesterone in an effort to reverse

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the effects of mifepristone, and conducted statistical analyses to determine the efficacies of different protocols compared to a control mifepristone embryo survival rate, derived from the literature.
***Results*: Intramuscular progesterone and high dose oral progesterone were the most effective with reversal rates of 64% ($P < 0.001$) and 68% ($P < 0.001$), respectively. There was no apparent increased risk of birth defects.**
***Conclusions*: The reversal of the effects of mifepristone using progesterone is safe and effective.**

Introduction

Medical induced abortion utilizing mifepristone has been available in the United States since 2000. In 2014, 31% of non-hospital induced abortions were medical induced abortions.[1] Some women decide to attempt to reverse the medical abortion process after taking mifepristone but before taking misoprostol, and inquire about the possibility of reversing the effects of mifepristone.[2]

The new FDA protocol, approved for medical abortion in 2016, involves the administration of mifepristone 200 mg orally as a single dose, which leads to embryonic or fetal demise, followed 24-48 hours later by misoprostol 800 mcg buccally as a single dose, which stimulates myometrial contractions. The protocol is approved up to 70 days after the first day of the last menstrual period.[3] Misoprostol is part of the protocol because mifepristone alone has an incomplete abortion rate of 20-40%, as determined by the end point of complete expulsion.[4]

Pharmacology

Mifepristone is a competitive antagonist of progesterone at the progesterone receptor (PR). It binds to the PR twice as avidly as progesterone.[5] Mifepristone is an orally active compound with a nearly 70% absorption rate, but its bioavailability is reduced to approximately 40% because of the first-pass effect.[6]

Demethylation and hydroxylation are catalyzed by CYP3A4; three metabolites retain biologic activity. The half-life of mifepristone is approximately 18-25 hours. Mifepristone and its metabolites can be measured up to 72 hours after an ingested dose.[5] The half-life of progesterone is longer, approximately 25-55 hours.[6,7]

Effects of Mifepristone

By blocking progesterone receptors, mifepristone leads to the separation of the decidua basalis from the trophoblast. This separation diminishes the oxygen and nutrients that can be delivered to the embryo or fetus by the maternal circulation and is the primary embryocidal and feticidal effect of mifepristone.[4,8,9]

In addition to this primary effect, mifepristone causes softening and dilatation of the cervix.[4] It also leads to myometrial contractions, increased myometrial sensitivity to prostaglandins[4,10] and the disinhibition of prostaglandin synthesis by the myometrium.[11]

Progesterone has been shown to have an autoregulatory effect on progesterone synthesis by the corpus luteum. Blocking progesterone receptors with mifepristone decreases progesterone secretion by the corpus luteum.[12]

Logic of Using Progesterone to Reverse Mifepristone Effects

Mifepristone is a competitive inhibitor of the progesterone receptor. It is well known that receptor agonism and antagonism are parts of a dynamic process that can be influenced by changing concentrations of the agonist or antagonist. Therefore, it makes biologic sense that increasing the progesterone levels in a pregnant woman by giving supplemental progesterone would favor the agonist progesterone effects and blunt the abortifacient effects of mifepristone.

An Animal Model

A Japanese rat study provides basic-science evidence of the ability of progesterone to negate the effects of mifepristone. In this experiment, one group of pregnant rats was given mifepristone while a second was given mifepristone and progesterone. In the group that only received mifepristone, only 33% of the pups survived. In the group that received mifepristone and progesterone, 100% of the pups survived. Furthermore, the first group had characteristic changes in the myometrium and ovaries; the group that received the combination had no such changes.[13]

Early Mifepristone Studies Reporting Continuing Pregnancy

When mifepristone was first studied as an abortifacient, misoprostol was not part of the protocol. During the 1980's, researchers determined that even though mifepristone was effective as an abortifacient, they believed it was necessary to add a prostaglandin analog to achieve a satisfactory complete uterine evacuation rate.[4] We must emphasize that the definition of incomplete abortion is incomplete emptying of the uterus.[14] Embryo or fetus survival is not implied.

The earliest studies also revealed that some embryos survived mifepristone. Baulieu, the principal developer of the drug, stated that at 4-7 weeks the percentages of efficacy of the regimen were approximately 70% for complete abortions, 20% for incomplete abortions and 10% for ongoing pregnancies (i.e., presumed embryo survival). For gestations 8-10 weeks, the comparable rates were 50% for complete abortions, 35% for incomplete abortions and 15% for embryo survival.[15]

In 2015, Grossman et al. published a review of the first case series of progesterone reversal of mifepristone, as well as 13 studies from the 1980's, addressing continuing pregnancies after mifepristone. The authors concluded that there was insufficient evidence to show that progesterone therapy improved survival over expectant management, based on the reported high ongoing pregnancy rates in some of these older studies.[16] However, closer scrutiny of the studies cited for high ongoing pregnancy rates reveals inadequate criteria for the diagnosis of continuing pregnancies. Many early researchers focused on an efficacy end point of complete uterine evacuation, and did not distinguish missed or incomplete abortions from continuing pregnancies (embryo or fetus

survival).[17] Only eight studies cited by Grossman had criteria sufficient to determine embryo survival and showed continuing pregnancy rates of 8-25%.[17]

A recent review found that 18 of the 30 articles investigating mifepristone monotherapy had adequate criteria to determine embryo survival.[17] After eliminating duplicate publications, 12 studies were identified which utilized follow-up ultrasound to distinguish between incomplete or missed abortion and embryo survival at the end of the study period. The mean percentage of embryos surviving mifepristone among all studies was 12.6%.[17] A single dose of 600 mg in five studies of early gestations 42-49 days in 493 subjects showed survivals of 9.4-17.1%.[17,18,19,20,21] Three studies of 58 women with gestations <49 days, using the current predominant 200-300 mg doses, noted embryo survival rates of 10-23.3%.[19,22,23,24] Four studies of 83 women included gestations up to 70 days, daily doses of 100-200 mg, and total doses 400-800 mg.; in three of these four studies, embryo survival was <25%.[25,26,27,28,29,30,31]

Methods

This is a retrospective analysis of clinical data of a group of pregnant women who took progesterone in an effort to reverse the effects of mifepristone. The study was reviewed and approved by an institutional review board. The lead author contributed clinical data from a variety of clinical settings across the United States and several other countries for comparison.

Subjects were pregnant women who had taken mifepristone, but had not yet taken misoprostol, and were interested in reversing its effects. Subjects called an informational hotline linked to an informational website and staffed by nurses and a physician assistant. After receiving information about the reversal process, those who decided to proceed with reversal were referred to physicians and mid-level practitioners in their respective geographic areas for treatment. The women gave written informed consent for treatment to their respective treating medical professionals that included permission to track their data. Data were collected from the women themselves and from their treating healtcare professionals.

Data were collected for different variables including gestational age at the time of mifepristone ingestion, mode of delivery of progesterone given, amounts of progesterone received, birth defects and preterm delivery. Progesterone was given in a variety of regimens by the 325 different medical professionals who treated these women. The modes of delivery of progesterone were intramuscular injection of progesterone in oil, oral administration of micronized progesterone, vaginal use of oral micronized progesterone capsules, compounded micronized progesterone vaginal suppositories, progesterone vaginal gel and progesterone vaginal suppositories.

We selected a 25% embryo or fetus survival rate, if mifepristone alone is administered, as a control because it is at the upper range of mifepristone survival rates and close to the 23% survival rate of the one early study that used a single 200 mg dose, the dose currently favored for medical abortions.[17] This study is designed to ascertain which progesterone treatments clinicians have offered to women seeking mifepristone

reversal that demonstrate efficacy beyond the 25% embryo survival rate, and compares the relative efficacies of different treatment protocols to the historic control.

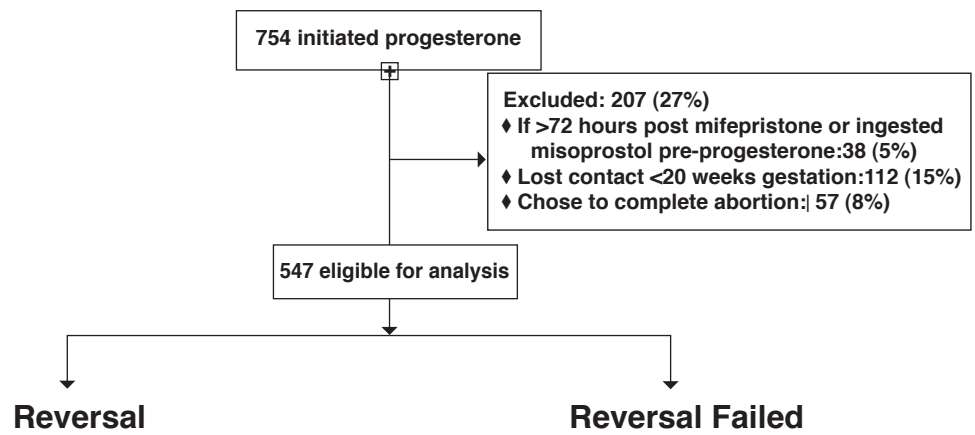
Results

From June 24, 2012 to June 21, 2016, 1,668 calls were received by the hotline from women who had taken mifepristone and were interested in reversal. Seven hundred fifty-four (45%) actually initiated progesterone therapy.

Subjects were included in the study if they were 72 hours or less post-mifepristone and had not taken misoprostol; 38 (5%) did not meet these criteria. Of the women who started progesterone therapy and met inclusion criteria, 116 (15.4%) were lost to follow-up at some point. Of those,112 (14.9%) were lost to follow-up prior to 20 weeks gestation and were excluded from the analysis. Four (0.5%) women remained pregnant with viable fetuses but were lost to follow-up after twenty weeks gestation and were included in the analysis as reversals.

Fifty-seven (7.6%) of the women, after starting progesterone therapy, changed their minds again and either took misoprostol to complete the medical abortion or procured surgical induced abortion. Of those 57, 39 (5.2%) chose to complete abortion medically with misoprostol, seven (0.9%) procured surgical abortions and 11 (1.5%) completed

Figure 1



abortion by unspecified means. These were not included in the analysis as they chose to no longer attempt reversal. See Figure 1.

Women who delivered babies after progesterone therapy or who were lost to follow-up after 20-weeks gestation were considered to have reversed their medical abortions, since any pregnancy loss after 20 weeks would be unlikely to be attributable to the early mifepristone exposure. The data analysis was accomplished using the Statistical Hypothesis Test on a population proportion.

After exclusions, there were 547 patients with analyzable outcomes who underwent progesterone therapy. There were 257 births (47%). Another four were pregnant with viable fetuses but were lost to follow-up after 20 weeks gestation (0.7%). The overall rate of reversal of mifepristone was 48%.

Two subgroups had the highest reversal rates. Those who received progesterone intramuscularly (IM) initially or exclusively had a 64% reversal rate. One subject in this group had an undocumented number of injections. The high-dose oral subgroup received oral progesterone, 400 mg twice a day for three days, followed by 400 mg once a day until the end of the first trimester and had a reversal rate of 68%, similar to the IM group. These survival rates compare favorably with published embryo and fetal survival rate of 25%, if no treatment is attempted,[17] the rate used as a control. See Table 1.

The gestational age at the time of ingestion was directly related to reversal success. See Table 2. This is not surprising since mifepristone embryocidal and feticidal rates fall with advancing gestational age.[33]

There was no correlation between maternal age and rate of reversal. In the subset of records noting time intervals, the time between mifepristone ingestion and the first progesterone dose was not statistically significant in relation to the success rate for reversals attempted within 72 hours of mifepristone injection.

Birth Defects

There were seven reported birth defects in the women who had reversals and follow-up after their deliveries for a rate of 7/257 (2.7%). See Table 3. This is equal to the birth defect rate in the general population of approximately 3%[34] and suggests that there is no increased risk of birth defects in babies born after mifepristone reversal.

Preterm Delivery

There were seven deliveries at <37weeks for a preterm delivery rate of 2.7%. The United States average is 10%.[35]

Multiple Gestations

There were nine sets of twins (4.3% of the pregnancies). There were no higher order multiples.

Discussion

Progesterone Safety

Progesterone is a naturally occurring hormone produced by the corpus luteum and by the placenta, and is essential for maintenance of the maternal fetal interface of pregnancy. It has been used safely in pregnancy for over 50 years.[36] The American Society of Reproductive Medicine states that no long-term risks have been identified when progesterone is used in pregnancy.[37] The FDA has given progesterone a category B rating in pregnancy, in contrast to synthetic progestins.[38]

Table 1: Reversals Compared to Reported Control of 25% Survival if No Treatment Undertaken

Progesterone Group	Number	Reversals	Reversal Failures	Percent Reversals	P Value	95% Confidence Intervals
All Groups	547	261	286	48%	<0.001	0.44-0.52
High Dose Oral	31	21	10	68%	<0.001	0.51-0.84
Intramuscular, All groups	125	80	45	64%	<0.001	0.56-0.72
IM, 1 Injection	50	24	26	48%	<0.001	0.34-0.62
IM, 2-5 Injec.	36	21	15	58%	<0.001	0.42-0.74
IM, 6-8 Injec.	9	9	0	100%	<0.001	0.67-1
IM, 9-10 Injec.	10	9	1	90%	<0.001	0.77-1.0
IM, 11 or More Injec.	19	17	2	89%	<0.001	0.76-1.0
Oral, All Groups	119	64	55	54%	<0.001	0.45-0.63
Oral Caps Vaginally, All Doses	156	61	95	39%	<0.001	0.31-0.47
Vaginal Suppository	34	11	23	32%	0.161	0.17-0.48

A recent retrospective study of a Danish infertility cohort suggested a possible increased risk of acute lymphocytic leukemia and sympathetic neural tumors in children born to mothers who had taken progesterone during pregnancy and before pregnancy. The increased risk was greatest in women who had taken progesterone for three or more cycles.[39] However, the infertility population examined in the Danish study, exposed to

Table 2: Gestational Age Compared to Reversal Rate

Gestational Age	Total	Reversal	Reversal Failure	Reversal %	*P* value	95% Confidence Intervals
5 weeks	76	19	57	25%	0.5	0.15-0.35
6 weeks	113	52	61	46%	<0.001	0.37-0.55
7 weeks	102	50	52	49%	<0.001	0.39-0.59
8 weeks	88	54	34	61%	<0.001	0.51-0.72
9 weeks	30	23	7	77%	<0.001	0.62-0.92

Table 3: Birth Defects

Birth Defect	Instances
Port Wine Stain	1
Bilateral Absent Toe	1
Unilateral Two Absent Fingers	1
Choroid Plexus Cyst	1
Cystic Kidney	1
Unilateral Failed Hearing Test	1
Heart Murmur	1

many cycles of progesterone and other medications, differs significantly from our population of fertile women who had a single exposure to progesterone.

Mifepristone Teratogenicity

While previous human studies are not large in number, the available evidence suggests that mifepristone is not teratogenic.[4,40,41] The American College of Obstetricians and Gynecologists (ACOG) Practice Bulletin March 2014 states that there is no evidence that mifepristone is associated with teratogenicity.[42] Our data set, the largest of babies exposed to mifepristone in utero, also indicates that the birth defect risk in women who have reversed mifepristone abortions is no higher than the risk in the general population.

Study Limitations

This study is limited in that it is not a randomized placebo-controlled trial. However, a placebo-controlled trial in the population of women who regret their abortion and

want to save the pregnancy would be unethical. Furthermore, although the number of women lost to follow-up was small, it could have affected the results. In addition, some data collection was incomplete.

One potential confounding variable is the use of ultrasound to select for living embryos prior to the first progesterone dose. It is possible that those embryos who were alive at the time of sonogram may have survived without progesterone therapy. However, our study also included some women who started progesterone therapy prior to sonographic documentation that the embryo was alive. Undoubtably, this group included women who already had an embryonic demise prior to initiation of progesterone therapy. Inclusion of these women would falsely lower the success rate of progesterone therapy. The numbers of women who received or did not receive ultrasound exams prior to initiating therapy were not available to our researchers. If ultrasound is readily available, sound practice would dictate that embryonic or fetal viability should be confirmed, or at least suggested, before treatment is started in order to avoid giving women progesterone unnecessarily and to exclude ectopic pregnancy before starting progesterone therapy.

Conclusions

The use of progesterone to reverse the effects of the competitive progesterone receptor blocker, mifepristone, appears to be both safe and effective. Progesterone therapy makes biologic sense, has been previously published as effective in an animal model and is supported by this case series which demonstrates a statistically significant difference in survival between treatment groups and the historic control. Mifepristone is embryocidal and feticidal but not teratogenic; progesterone is not associated with birth defects.

Based on these new data, two reasonable protocols can be suggested for women who seek to reverse the effects of mifepristone:

1. Progesterone micronized 200 mg capsule two by mouth as soon as possible and continued at a dose of 200 mg capsule two by mouth twice a day for three days, followed by 200 mg capsule two by mouth at bedtime until the end of the first trimester; and

2. Progesterone 200 mg intramuscular as soon as possible and continued at a dose of 200 mg intramuscular once a day on days two and three, then every other day for a total of seven injections. Some clinicians may choose to continue intramuscular treatment longer since this recommendation is based on relatively small numbers.

Recommendations for Future Research

We propose that further research employing randomized controlled trials comparing progesterone doses and routes of administration are needed to confirm which mode of delivery, dose and duration of progesterone therapy is most efficacious and carries the least burden for the patient.

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Delgado Letter to the Editor 12.14.2019

Attachment 4

Press Release

13 December 2019

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Regarding the Creinin et al Mifepristone antagonization study (1), we wish to challenge some of the authors' conclusions regarding the safety and efficacy of progesterone used to reverse the effects of mifepristone in women who change their minds after starting a medical abortion. This study does make it clear that taking mifepristone and doing nothing else does pose a risk to the pregnant woman.

It should be noted that among the twelve subjects, the one who required the blood transfusion and suction aspiration (surgical abortion) was in the placebo group and did not receive progesterone. Two other subjects were transported by ambulance to the emergency department. One, in the progesterone group, represented a failed abortion reversal. For "brisk bleeding" she called the ambulance. In the emergency department, she was noted to have completed her abortion and did not require suction aspiration. The third patient was in the placebo group, was transported by ambulance, and required suction aspiration.

Two voluntarily exited the study. One patient, in the placebo group, "had increased anxiety about bleeding . . . and requested a suction aspiration." The other patient who voluntarily exited the study was in the progesterone group and had increased nausea and vomiting, requiring intravenous fluids as an outpatient. She also requested a suction aspiration.

Therefore, the only patients who required (not requested) suction aspiration before completing the study were in the placebo group. The progesterone patient with nausea and vomiting requested the suction aspiration and the one with the failed reversal did not have a suction aspiration.

As for effectiveness, after excluding the two who voluntarily withdrew from the study (one in the placebo group and one in the progesterone group), four of the five (80%) who received progesterone had surviving embryos. This is consistent with Delgado et al's 2018 study with a 68% live birth rate after treatment with the same oral progesterone protocol used in the Creinin study. (2) The embryo survival of two of five (40%) in the placebo group is consistent with the historic survival rate of 25% for embryos exposed to mifepristone only in the early studies conducted before misoprostol was added to the medical abortion regimen.(3) An "intention-to-treat" analysis that includes the two who voluntarily exited shows four of six (67%) embryos in the progesterone group survived, while only two of six (33%) in the placebo group survived.

This study, although not reaching statistical significance, certainly supports the earlier research demonstrating the effectiveness of using progesterone in women who wish to reverse their mifepristone abortions. This study also demonstrates the hazards of having a placebo group which, from a maternal safety standpoint, fared poorly compared to the progesterone group.

George Delgado, MD
Mary Davenport, MD
Matthew Harrison, MD

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